
**Human Research Program
Human Health Countermeasures Element
Cardiovascular Risks
Standing Review Panel (SRP)
Final Report**

November 2009

I. Executive Summary & Overall Evaluation

The Cardiovascular Risk Standing Review Panel (SRP) evaluated several cardiovascular risks associated with space flight along with the ongoing and emerging plans to study these issues and potentially propose and/or develop countermeasures. The areas of focus included: 1) The risk of cardiac rhythm problems during prolonged space flight, and 2) Issues related to the risk of orthostatic intolerance during re-exposure to gravity. An emerging area of concern is radiation associated vascular injury.

The risk of cardiac rhythm disturbances has emerged based on case reports only. No systematic study of this risk has been published. However, concerns about this risk are heightened by the age range of astronauts, the structural changes in the heart that occur during space flight, and the potential shifts in fluids and electrolytes. The current plan is to use prolonged Holter monitor EKG records made as part of the “Integrated Cardiovascular SMO” in space to determine more about the frequency and magnitude of this problem and to link this data to complementary data from the nutrition group on electrolytes. The SRP was supportive of this approach. The SRP also felt that any data related to cardiovascular risk in space should be better coordinated with the medical screening data that all astronauts undergo at regular intervals. Additionally, while there are potential privacy issues related to this suggestion, many of the current barriers to better coordination of experimental and clinical data appear to reflect longstanding cultural traditions at NASA that need rethinking.

The risk of orthostatic intolerance during re-exposure to gravity was seen by the SRP as an area supported by a wealth of published physiological evidence. The SRP also felt that moving forward with the planned approach to countermeasures was reasonable and that extensive additional hypothesis testing on the physiology of orthostatic intolerance was not needed at this time. There was support for developing ground based models of limited (e.g. 1/6th) G environments on Earth that generated a number of ideas for consideration by NASA investigators.

The SRP identified three readily implemented approaches to manage orthostatic intolerance:

1) The SRP discourages the use of promethazine (Phenergan) to treat nausea after return to 1G. Safer anti-nausea medications are available that do not exacerbate orthostatic intolerance, adversely affect performance and are which are not subject to “black box” warnings.

2) The SRP is concerned about the potential for heat stress on astronauts during re-entry and egress, with its concomitants of orthostatic intolerance and performance deficits. If heat stress is documented, efforts to improve astronauts cooling during re-exposure to gravity should be a high priority.

3) The SRP recommends NASA optimize carbohydrate, salt and fluid intake of astronauts before landing for volume maintenance.

A new risk for consideration focused on atherosclerosis during exploration class missions due to radiation or oxidative damage. The SRP felt this risk should be fully scoped and ideas generated about how it might be studied.

In summary, the SRP was supportive of the approach outlined by NASA scientists and administrators on the two major areas of cardiovascular risk. This support acknowledges the operational and logistical constraints associated with marrying science and space flight. A third, new, risk (radiation and vascular injury) was identified. On a more general level, the SRP felt that better coordination of experimental and clinical data across NASA “silos” would be helpful at multiple levels. Additionally, many of the data sets contain small numbers of subjects with “responders and non-responders” and analytical approaches that focus the mechanisms behind the individual variability that might be used to better understand the interactions of the microgravity environment and various interventions.

II. Critique of Gaps

RISK OF CARDIAC RHYTHM PROBLEMS

GAPS:

The SRP affirmed the importance of the identified and new gaps. Some of these gaps lack adequate data and among some of the current tasks there is a lack of coordination with clinical screening data. The plan to collect more data is reasonable. The need to better coordinate data collected in space with the “medical record” needs attention at a management level.

Coordination of data collected with the nutrition and exercise risk groups is essential. In particular, data on carbohydrate, sodium and caloric intake during the two days prior to landing should be compared with the occurrence of postural hypotension.

CV1: What are the in-flight alterations in cardiac structure and function?

The SRP agrees that this is an area worthy of study.

CV7: How are fluids redistributed in flight?

The SRP agrees that this is an area worthy of study. It is also an area where animal data can be translated to humans, for example, how changes in blood pressure gradients affect specific organs or vascular bed. Examples include:

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- Muscle/bone effects including changes in limb venous pressure and bone loss.
 - Hypertrophy of cranial blood vessels in simulated microgravity.
 - Atrophy of lower limb arterioles in simulated microgravity.

CV8: Can manifestations of sub-clinical or environmentally-induced cardiovascular diseases during spaceflight be predicted?

The SRP believes that better coordination with data from medical screening is critical to addressing this issue.

N7: What are the potassium, magnesium and phosphorus changes in relation to cardiovascular issues and bone loss?

The ongoing collaboration with the nutrition group should permit this gap to be addressed. It appears unlikely that space flight would cause electrolyte alterations sufficient to be a cardiovascular risk in astronauts with normal endocrine and renal function.

RISK OF ORTHOSTATIC INTOLERANCE DURING RE-EXPOSURE TO GRAVITY

GAPS:

This area was seen as relatively mature from a scientific perspective with reasonable countermeasures in the planning or implementation stage. A major concern is potential concurrent heat stress which is known to reduce orthostatic tolerance and have a negative synergistic effect with de-conditioning/bed rest. An investigation is recommended to identify the extent to which environmental and physiological factors associated with re-entry/landing result in a heat load to the astronauts. If such a heat stress is identified, efforts to improve astronauts cooling during re-exposure to gravity should be a high priority.

Promethazine (Phenergan) is sometimes used to treat nausea after return to 1G. The SRP discourages use of this agent because:

- Promethazine can have an adverse interaction with midodrine, an agent that may be useful to prevent orthostatic intolerance.
- Central depressants such as promethazine may exacerbate orthostatic intolerance.
- Phenothiazines such as promethazine interfere with psychomotor coordination and may adversely affect performance tests.
- Parenteral administration of promethazine carries sufficient risk to be the subject of a black box warning.
- Safer anti-nausea medications that do not have the above disadvantages are available.

CV3: Is orthostatic intolerance a potential hazard?

The SRP agrees that orthostatic intolerance is a risk.

CV4: Is 1/6-g exposure protective of 1-g orthostatic tolerance?

The SRP believes that developing a useful human bed rest model related to the gap is worthwhile, but raised issues for NASA to consider as this model is developed.

NEW RISK:**Risk of Atherosclerosis during Exploration Class Missions Due to Radiation or Oxidative Damage.**

The SRP felt this risk should be fully scoped and ideas generated about how it might be studied.

III. Critique of Tasks***RISK OF CARDIAC RHYTHM PROBLEMS*****GAPS:**

The main gaps in this area are twofold. First, there is a relative lack of published hard data on the incidence and timing of cardiac arrhythmias during space flight. There appear to be data at the “case-report” level but no comprehensive data in a large number of subjects collected repeatedly over relatively long time periods. The plans to address this issue as part of the data collected via the Integrated Cardiovascular SMO are a reasonable approach to this data gap. Second, if arrhythmias emerge as a problem during prolonged space flight, it will be critical to coordinate these data with clinical screening data to gain insight into what (if any) screening tests might predict the development of arrhythmias during space flight. The SRP also noted that Holter monitor data can be analyzed to screen for sleep disordered breathing which would be of interest.

CV1: What are the in-flight alterations in cardiac structure and function?

The SRP was supportive of the Integrated Cardiovascular SMO (Bungo/Levine Directed Study). Highlights include:

- Prolonged EKG Holter data, structure/function data via echocardiography.
- The SRP noted the possibility of sleep apnea screening by Holter.

Areas for better integration with other Risk Panels include “Multisystem Effect of Exercise: Integrative CM Development” (Levine)

CV7: How are fluids redistributed in flight?

The SRP agreed with the assessment, and felt there was no need to increase priority. The panel was supportive of the two tasks:

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- Bracelet (Dulchavsky) – NSBRI
 - Braslet (Duncan) – ExMC

CV8: Can manifestations of sub-clinical or environmentally-induced cardiovascular diseases during spaceflight be predicted?

As noted in several places in this report, the SRP felt that collecting and analyzing additional data on these topics was worthwhile and much of it was going to be accomplished as part of the Integrated Cardiovascular SMO (Bungo/Levine Directed Study). The SRP also noted the need to integrate any in-flight or post-flight findings with clinical data from astronaut screening. Areas of screening that might prove useful include:

- MRI/echo screening for rare conditions such as RV dysplasia and hypertrophic cardiomyopathy that predispose to arrhythmias.
- Maximal stress test for arrhythmias during astronaut screening.
- Better communication with flight surgeons about optimal screening and frequency.
- Additional emphasis on how behavioral health affects CV function –sleep deprivation, markers of mental/emotional distress, etc..

N7: What are the potassium, magnesium and phosphorus changes in relation to cardiovascular issues and bone loss?

The SRP felt that the Nutrition SMO (Smith Directed Study) would provide the needed data and there was ongoing evidence of collaboration between the Nutrition and CV groups.

- Electrolyte data from the Nutrition SMO.
 - The nutrition data highlighted the need for analytical approaches that focus on the mechanisms behind the individual variability. Such an approach may be used to better understand the interactions of microgravity environment and various interventions.

RISK OF ORTHOSTATIC INTOLERANCE DURING RE-EXPOSURE TO GRAVITY

GAPS:

CV3: Is orthostatic intolerance a potential hazard?

The SRP agrees that orthostatic intolerance is a potential hazard and felt that the data presented or that is being collected as part of the following studies/projects has value:

- Hypovolemia Study (Platts, Directed Study)
- Gender Differences (Platts NRA)
- Midodrine SMO (Platts Directed Study)
- Evaluate alternate pressure garments (Platts, Directed Study)
- Jobst Flight Eval (Platts/Locke, Directed Study)
- Integrated Cardiovascular SMO (Bungo/Levine Directed Study)

Areas that the SRP felt needed attention include:

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- Issues related to compression garments and long duration flight.
 - Verify utility of compression garments after long duration flight.
 - Resolve technical issues for compression garments.
 - Coordinate with nutrition to optimize carbohydrate, salt and fluid intake before landing for volume maintenance.
 - Reduce heat loads on astronauts during landing/egress.
 - Verify the utility of hypovolemic screening of astronauts to determine if tilt testing during hypovolemia can predict subjects prone to orthostatic intolerance.

CV4: Is 1/6-g exposure protective of 1-g orthostatic tolerance?

The SRP felt this issue was of interest in the context of several ongoing areas of investigation including:

- CV Alterations during Lunar Missions (Platts NRA)
- Lunar Analog development (Directed Study)

However, several issues related to the Lunar Analog Study came up during discussion:

The Lunar Analog as is appropriate for study of bone/muscle. However, use of the Lunar Analog to study orthostatic hypotension incorporates adjustments (e.g., use of stockings) that bring the model into question.

The SRP had concerns about the digital astronaut model predicting hypovolemia in 1/6G.

At this early stage in the development of the Lunar Analog protocol the bedrest group will need to consider several models and see which ones are practical and relevant; and which one will answer pertinent questions. They may decide to use a simple model that will answer basic questions or a model that mimics an actual flight, such as one to the moon. The latter would include a micro-G stage, fractional-G exposure and return micro-G stage.

RISK OF ATHEROSCLEROSIS DURING EXPLORATION CLASS MISSIONS DUE TO RADIATION OR OXIDATIVE DAMAGE

NSBRI is supporting two studies on this problem, and the SRP is supportive of this.

IV. Discussion on the strengths and weaknesses of the IRP

The Cardiovascular Risk SRP had no issues with the Integrative Research Plan or the risks and gaps identified. Specific recommendations concerning tasks are given in Section III.

V. Discussion of Element Specific Questions in Addendum and/or Any Other Issues or Concerns the Panel Chooses to Address.

1. Are there obvious, unrealistic aspects in the IRP schedule?

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- The SRP had no concerns about expectations.
2. Is the portfolio of tasks sufficiently complete to acquire an adequate description of the risks? For example, will “space normal” be adequately defined?
 - The SRP felt that the tasks were generally well matched, complete and had adequate descriptions of risk. Suggestions for modifications in some protocols and experimental designs were discussed and have been highlighted above. The need to coordinate with medical data is seen as critical.
 3. Is the portfolio of tasks developing the appropriate technologies?
 - In general yes, however the SRP felt that the use of alternate data analysis approaches might permit a better understanding of responders and non-responders and provide more insight into how best to implement a series of countermeasures. The key is to look for commonalities among astronauts who have limited cardiovascular deterioration during space flight, and to link the CV, exercise, nutrition and medical data to see if critical pathways can be identified.
 4. Does the portfolio contain a sufficient number of countermeasure development tasks?
 - Yes
 5. Is the portfolio properly balanced among risk description, countermeasure development and technology development activities?
 - The SRP had no concerns about risk description, countermeasure development and technology development activities. We did highlight the need to consider the role of concurrent thermal stress and how it might impact issues related to orthostatic intolerance on re-entry.
 6. Are the appropriate analogs being used?
 - In general, the SRP felt that the ground-based analogs were reasonable. There were some concerns about the 1/6G bed rest model that we detailed above.
 7. Is it reasonable to begin countermeasure work prior to complete description of risks?
 - The SRP identified areas where this would be appropriate and where more information would be needed to begin to develop countermeasures.

VI. Cardiovascular Risk SRP Charge

The SRP is chartered by the Human Research Program (HRP) Program Scientist at the NASA Johnson Space Center (JSC). The purpose of the SRP is to review and provide analysis on the status and progress of HRP Elements and Projects. Your report will be provided to the HRP Program Scientist and will also be given as a courtesy to the HHC Element and Projects at JSC.

The SRP should (to the fullest extent practicable):

1. Evaluate the ability of the Integrated Research Plan (IRP) to satisfactorily address the risks by answering the following questions:
 - A. Have the proper Gaps have been identified to address the Risks?
 - i) Are all the Gaps relevant?
 - ii) Are any Gaps missing?
 - B. Have the proper Tasks been identified to fill the Gaps?
 - i) Are the Tasks relevant?
 - ii) Are any Tasks missing?
2. Identify the strengths and weaknesses of the IRP, *and* identify remedies for the weaknesses, including answering these questions:
 - A. Are the risks addressed in a comprehensive manner?
 - B. Are there obvious areas of potential integration across disciplines that are not addressed?
3. Address (as fully as possible) the questions provided in the charge addendum and to comment on any additional information provided to the Panel that is not addressed in #1 or #2 above.
4. Expect to receive review materials at least five weeks prior to the site visit.
5. Participate in a SRP teleconference to discuss any issues, concerns, and expectations of the review process approximately three weeks prior to the face-to-face meeting
 - A. Discuss the SRP charge and address questions about the SRP process
 - B. Identify any issues the SRP would like to have answered prior to the site visit
6. Attend the SRP meeting and tour at NASA/JSC
 - A. Attend Element and risk panel presentations, question and answer session, and briefing
 - B. Prepare a draft report including recommendations from the SRP that will be briefed to the Program Scientist by the SRP chairperson or panel. The report should address #1 and #2 above, the questions in the charge addendum, and any other information considered relevant by the SRP.
7. Prepare a final report (within one month of the site visit) that contains a detailed evaluation of the risks and provides specific recommendations that will optimize the scientific return to the HRP. The final report should provide a comprehensive review of Item #1 and #2 above, address the questions in the addendum to the charge, and any additional information the SRP

would like to provide.

8. Consider the possibility of serving on a non-advocate review panel of a directed research proposal or on a solicited research peer review panel; or otherwise advise the Program Scientist.

Addendum to charge: (Element Specific Concerns):

3. Are there obvious, unrealistic aspects in the IRP schedule?
4. Is the portfolio of tasks sufficiently complete to acquire an adequate description of the risks?
 - a. For example, will “space normal” be adequately defined?
8. Is the portfolio of tasks developing the appropriate technologies?
9. Does the portfolio contain a sufficient number of countermeasure development tasks?
10. Is the portfolio properly balanced among risk description, countermeasure development and technology development activities?
11. Are the appropriate analogs being used?
12. Is it reasonable to begin countermeasure work prior to complete description of risks?

VII. Cardiovascular Risk SRP Roster

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